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Covariate Assessment of T-wave Morphology and QTc prolongation: New Opportunities in the Evaluation of Drug-induced ECG Changes

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QTc prolongation due to the administration of a drug is not a reliable surrogate of the drug's proarrhythmic potential. Consequently, the development of suitable indices for the characterization of drug-induced repolarization changes might greatly improve risk assessment of new and existing compounds. This study adds a T-wave morphology composite score (MCS) to the QTc interval evaluation of drugs affecting cardiac repolarization.

Electrocardiographic recordings from 62 subjects on placebo and 400 mg moxifloxacin were compared to recordings from 21 subjects receiving 160 and 320 mg d,l-sotalol. The antibiotic drug, moxifloxacin has a favorable cardiovascular safety profile and is recommended as a positive control in thorough QT studies. In contrast, the antiarrhythmic drug d,l-sotalol has a less favorable safety profile with a reported incidence of TdP between 1.8% and 4.8%.

This difference in risk profiles between moxifloxacin and d,l-sotalol is indicated by T-wave morphology changes, as assessed by ΔMCS. T-wave morphology changes are larger for 320 mg d,l-sotalol than for 160 mg d,l-sotalol, which are again larger than for moxifloxacin and placebo. Covariate analyses of ΔQTc and ΔMCS showed T-wave morphology changes as a significant effect of dl-sotalol. In contrast, there is no effect of moxifloxacin on T-wave morphology (ΔMCS) at any given change in QTc.

This study offers new insights into the repolarization behavior of a drug with low cardiac risk versus a high risk drug and suggests added benefits of a T-wave morphology composite score as a covariate to the assessment of the QTc interval.

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